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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/785,497	02/24/2004	Mark W. Becker	249.P2	9922

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EXAMINER	
MARTIN, PAUL C	
ART UNIT	PAPER NUMBER
1657	
MAIL DATE	DELIVERY MODE
12/09/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/785,497	BECKER ET AL.	
	Examiner	Art Unit	
	PAUL C. MARTIN	1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 September 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-13 and 15-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-13 and 15-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 3-13 and 15-17 are pending in this application and were examined on their merits.

With this New Non-Final Rejection, the Finality of the Rejection filed 10/24/07 is withdrawn in view of the New Rejections below.

The rejection of Claims 1, 3-7 and 10-13 under 35 U.S.C. § 103(a) as being unpatentable over Shaw *et al.* (1997) has been withdrawn in view of the New Rejections below.

The rejection of Claims 1, 3-7, 9-13, 15 and 16 under 35 U.S.C. § 103(a) as being unpatentable over Shaw *et al.* (1997) in view of Glazier *et al.* (US 5,627,165) has been withdrawn in view of the New Rejections below.

The rejection of Claims 1, 3-8, 10-13 and 17 under 35 U.S.C. § 103(a) as being unpatentable over Shaw *et al.* (1997) in view of Starrett *et al.* (US 5,663,159) has been withdrawn in view of the New Rejections below.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3-13 and 15-17 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 requires the selection of at least one therapeutic target tissue. It is unclear what about the target tissue makes it therapeutic and if so, how it is therapeutic especially with regard to non-target tissue. Claims 3-13 and 15-17 are rejected as being dependent upon rejected Claim 1.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3-7 and 11-13 are newly rejected under 35 U.S.C. § 103(a) as being unpatentable over Shaw *et al.* (1997) in view of Cook *et al.* (1995).

Shaw *et al.* teaches a screening method comprising the steps of; providing an amino acid phosphonoester prodrugs of PMPA (Pg. 1825, Table 1), selecting two tissues (liver and intestine), administering the prodrug to both and determining the relative *in vitro* biological stability and bioavailability of PMPA in the samples (Pg. 1827, Column 1, Lines 7-8 and Column 2, Lines 1-14 and Table 3, and Pg. 1828, Column 1, Lines 1-10).

Shaw *et al.* teaches wherein the prodrug of PMEA was shown to significantly increase the oral bioavailability of PMEA in HIV infected patients and wherein PMPA has selective and potent inhibitory activity *in vitro* against retroviruses and wherein IV PMPA has been shown to reduce viral load in HIV infected patients (Pg. 1824, Column 2, Lines 1-9 and 16-18).

It is inherent in the method of Shaw *et al.* that the screening method would determine the relative antiviral activity conferred by the PMPA prodrug in the samples because PMPA is a known potent antiviral compound and the determination of the biological stability and bioavailability of prodrug derived PMPA in various tissues and bodily fluids would necessarily also provide a determination of the *relative* antiviral activity of the prodrug in those tissues and fluids even if no virus were present.

Shaw *et al.* does not teach a method wherein the target tissue is not small intestine.

Cook *et al.* teaches a method wherein anti-HIV ester-prodrugs are administered to several different species and determining the biological stability and bioavailability of the prodrug in small intestine and liver fractions as well as whole blood, red blood cells and plasma (Pg. 1161, Figs 2-4). Cook *et al.* further teaches that ester-type drugs and prodrugs are hydrolyzed by esterase enzymes present in intestinal mucosa, tissues (e.g. liver, kidney, eye) and blood, and the pharmacological activity and toxicity of the esters are markedly affected by the degree of hydrolysis. The reference states that esterase activities in tissues are known to vary between species and that the purpose of the study was to determine whether species differences in bioavailability is due to species differences in ester hydrolysis rate or absorption of the prodrug itself as well as to determine the site(s) of ester hydrolysis (liver, intestine, RBC, plasma) (Pg. 1158, Column 2, Lines 24-40).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the method of Shaw *et al.* to select a target tissue and non-target tissue wherein the target tissue is not small intestine because while the claimed invention excludes the use of small intestine and therefore excludes the reference as prior art for purposes of anticipation, the reference is still valid for all its teachings with regard to the obviousness of the claimed invention. Cook *et al.* teaches that it was well known at the time of the invention to screen various tissues and bodily fluids of different species for prodrug hydrolysis and that variations were known among both the site and degree of hydrolysis among species.

Therefore, this type of tissue screening was well known at the time of the invention and it would have been desirable and well-within the purview of one of ordinary skill in the art to substitute another tissue such as liver, kidney, eye, etc. in place of the target tissue small intestinal homogenate in order to screen for the site of prodrug hydrolysis as well as bioavailability and biostability of the prodrug in those other tissues within a species. One of ordinary skill in the art would have been motivated to make this modification because of the ability to screen for the site (target tissue) of prodrug enzymatic hydrolysis as well as the bioavailability and biostability of prodrugs in various non-target tissues in different animal models. There would have been a reasonable expectation of making this modification because Shaw *et al.* teaches the use of two tissues as well as blood and Cook *et al.* teaches that prodrug screening in multiple tissues and blood fractions was well known in the art at the time of the invention.

Claims 1, 3-7, 9-13, 15 and 16 are newly rejected under 35 U.S.C. § 103(a) as being unpatentable over Shaw *et al.* (1997) in view of Cook *et al.* (1995) and further in view of Glazier *et al.* (US 5,627,165).

The teachings of Shaw *et al.* and Cook *et al.* were discussed above.

Neither Shaw *et al.* nor Cook *et al.* teach selecting a prodrug having a relative activity in the target tissue that is greater than 10 times that of the non-target tissue; wherein the target and non-target tissues are in an animal, the prodrug is administered to the animal and the relative activity is determined by analysis of the animal tissues after administration of the prodrug; wherein the target tissue is lymphoid tissue and the activity is anti-HIV activity or wherein the target tissue is liver and the activity is anti-HBV activity.

Glazier *et al.* teaches a method of screening for antiviral activity of PMEA [9-(2-phosphonylmethoxyethyl)adenine] prodrugs on HIV infected human T-lymphocyte (lymphatic tissue) (CEMss) and HBV infected hepatocytes (liver tissue) and by administering the prodrug to a target tissue (HIV/HBV infected) and a non-target (uninfected) control; and determining the antiviral activity conferred by the prodrug on the tissues and selecting a prodrug having an activity in the infected tissue greater than 10 times that if the non-infected tissue. (Column 36, Lines 35-48 and Column 37, Lines 5-22 and Columns 38 and 39, Tables).

Glazier *et al.* teaches wherein mice are administered with a dansyl phosphonate prodrug and the relative activity of the prodrug in blood, liver, spleen and kidney samples is determined wherein the levels of relative activity of the pro-drug are at least 10 times greater in the liver than in the spleen (Column 41, Lines 44-67 and Column 42, Lines 1-27 and Figs 7C and 9C).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the screening method to determine the bioavailability and biostability of PMPA prodrugs as taught by Shaw *et al.* and Cook *et al.* above with the method of screening for antiviral activity of phosphonoamidate prodrugs of Glazier *et al.* because one of ordinary skill in the art would have recognized that both methods are drawn to the determination of the relative antiviral activities of phosphonoamidate prodrugs in various tissue types. One of ordinary skill in the art would have been motivated to make this combination because of the advantage demonstrated by Glazier *et al.* of being able to directly determine the specific antiviral activity of the prodrugs against specific viruses in specific target tissues, such specificity not being determined in the method of Shaw *et al.* and Cook *et al.* which only determined the relative general antiviral activity in target tissues. There would have been a reasonable expectation ofsuccess in making this combination because both methods are drawn to the characterization of the levels of antiviral activity seen during the administration of phosphonoamidate prodrugs to animal tissues.

Claims 1, 3-8, 11-13 and 17 are newly rejected under 35 U.S.C. § 103(a) as being unpatentable over Shaw *et al.* (1997) in view of Cook *et al.* (1995) and Starrett *et al.* (US 5,663,159).

The teachings of Shaw *et al.* and Cook *et al.* were discussed above.

Neither Shaw *et al.* nor Cook *et al.* teach wherein the phosphonoester is an aryl ester, or wherein the target tissue is hematological and the activity is antitumor activity.

Starrett *et al.* teaches the administration.of an aryl ester phosphonoester PMEA prodrug to rats and assaying the amount of metabolite of the parental prodrug PMEA that is bioavailable based on urine excretion data (Column 9, Lines 59-67 and Column 10, Tables).

Starrett *et al.* teaches wherein PMEA was found to have anti-tumor activity against intraperitoneal P388 leukemia (Column 2, Lines 40-41).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the screening method to determine the bioavailability and biostability of PMPA prodrugs in various tissues as taught by Shaw *et al.* and Cook *et al.* above with the method of Starrett *et al.* for determining the metabolism of an aryl ester prodrug with anti-tumor activity in rats because both methods are directed to the bioavailability of phosphonamidate prodrugs in animals because both methods are drawn to the metabolism and pharmacokinetics of phosphonate nucleoside analogs having antiviral and/or anti-tumor activities.

One of ordinary skill in the art would have been motivated to make this combination because Shaw *et al.* and Cook *et al.* already teaches wherein the target tissue was hematological or other tissue and the activity was antiviral and combination of the method of Starrett *et al.* which teaches the use of the aryl ester prodrug of PMEA would provide an assessment of the relative anti-tumor activity in both the target tissue and non-target tissues. There would have been a reasonable expectation of success in combining these two methods because both are drawn to the characterization of the metabolism and bioavailability of prodrugs in animals.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

No Claims are allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure:

Biesson *et al.* "Novel hepatotrophic prodrugs of the antiviral nucleoside 9-(2-phosphonylmethoxyethyl) adenine with improved pharmacokinetics and antiviral activity"; FASEB Journal, Vol. 14, No. 12 (2000) pp. 1784-1792.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to PAUL C. MARTIN whose telephone number is (571)272-3348. The examiner can normally be reached on M-F 8am-4:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Paul Martin
Examiner
Art Unit 1657

12/02/08

/JON P WEBER/

Supervisory Patent Examiner, Art Unit 1657